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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,888	07/14/2003	Donald Jeffery Zack	01107.00369	3409

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,888	ZACK ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06-26-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 10 and 12-19 have been amended; claims 1-9 and 20-53 have being cancelled by amendment filed on 06-26-2006. Currently claims 10 and 12-19 are pending for examination.

Information Disclosure Statement

3. The information disclosure statements filed on 06-26-2006 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies. The information disclosure statement filed on 06-26-2006 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Those citations not considered by the examiner will have a line drawn through the citation and citations considered will have the examiner's initial adjacent thereto. A submission of a legible copy of each cited non-patent literature publication or that portion which caused it to be listed is required for examination.
4. The examiner notes that applicant has incorrectly used the term axotomy as "axiotomy" on p. 54, defined as causing neuronal cell death.

Response to arguments

5. Withdrawn rejections in response to Applicant arguments or amendments:

Drawings Objection

In view of Applicant's amendment to the specification to refer to content presented in Tables 1-9 as "tables" rather than "figures" the objection to the drawings has been withdrawn.

Claim Rejections - 35 USC § 112- First paragraph- Written description

In view of Applicant's amendment to claim 10, rejections of claim 10 and dependent claims 12-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn.

6. Remaining objections in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112- Second paragraph-

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, and 12-19 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 (and dependent claims) is indefinite in its recitation of "reducing" since it is unclear how this term is defined, what its metes and bounds are, or to what the term is directed towards. It is not clear whether preventing refers to prevention of quiescent stages of cell death, which persists below the threshold in most cells, or the eminent cell death as a result of diverse activating stimuli (Davis, 2001, Curr Opin Investig Drugs. 2001, p. 654, col. 2, last paragraph).

Claim Rejections - 35 USC § 112- First paragraph-Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 12-19, remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make an/or use the invention.

The specification does not reasonably provide enablement for claims directed to a method of reducing neuronal cell death in a mammal comprising administering to said mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to reduce cell death in any human disease associated with

neuronal cell death (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders).

In response to applicant's assertion (Remarks, p. 50, paragraph 1) that the weight of evidence, including the teachings of the specification and the prior art –and including the references cited in the rejection- favors the conclusion that claims 10 and 12-19 are enabled, the comment is not found persuasive. Applicant traverses the rejection by discussing the following *Wand* factors.

The nature of the invention and the breadth of the claims.

First, on page 50 of Remarks, Applicant argues that the claims recite administration of the nucleic acid molecules to a mammal and are therefore no limited to human administration. Such is not persuasive.

The claims when given the broadest reasonable interpretation encompass a human subject since human subjects are classified in the animal kingdom as vertebrate mammals. Further, the claims recite a number of neuronal diseases associated preferentially with human subjects (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders). Hence, a mammal can be reasonably construed as a human subject.

Secondly, on page 50 of Remarks, Applicant argues that the Office Action consistently misconstrues the claims as requiring the use of a non-viral vector and that the claims are not so limited since claims recite "administering to the mammal a nucleic acid molecule comprising a coding sequence..." . Such is not persuasive.

As discussed in the previous office action, though the specification states, " nucleic acids and the corresponding encoded proteins markers of the present invention can be used therapeutically in a variety of modes (p. 45, [46]), the specification does not provide any specific and substantial or well-established use comprising administering a nucleic acid molecule expressing a neuronal marker of the elected species invention (e.g., NM androgen binding protein). Therefore, the method claims 10, 12-19 are interpreted as being drawn non-viral therapeutic preventions.

State of the prior art

Applicant argues on p. 51 of remarks that the sate of the art of gene therapy in 1995-1999 is not relevant to whether the claimed method was enabled at this application's July 15, 2002 priority date, and that only the art in July 2002 is relevant to the enablement of claims 10 and 12-19. To support this assertion, Applicant files new referenced published from 1991 to 2002 to prove that the state of the prior art is enable for a method of reducing neuronal cell death in a mammal using nonviral systems and viral systems. Such is not persuasive.

The lack of predictability of the nonviral gene therapy was discussed in the previous office action. Applicant submitted references further corroborate the unpredictability of the art in the use of nonviral gene therapy as a method of reducing neuronal cell death in a mammal. The teachings of Hecker et al., (2001, Mol. Ther. 3:375-84) represent one example of these knowledge wherein gene delivery is accomplished by using optimized formulations to overcome the inability of plasmid DNA –cationic lipid complex to target specific cells for transient expression.

Additionally, Applicant has submitted a number of references as confirmation of effective *in vivo* exogenous viral gene expression in neurons as proof of enablement for the methods set fort and claimed in the instant invention. Such is not persuasive.

Though the state of prior art teaches specific examples of gene transfer mediated by adenovirus, herpes simplex virus and/or retrovirus vectors, specific concerns have to be addressed in relation to the safety of said vectors. It was well known in the art at the time this application was filed that the immune reaction to adenovirus is potent. For example, Blits et al., (Cell Transplantation, 2002) teach that direct gene transfer in the nervous system was first achieved with herpes viral and E1-deleted adenoviral vectors, however Blits et al., disclose that both vector systems are problematic in that these vectors elicit immunogenic and cytotoxic responses. Further, Blits et al., teach that central to the success of gene therapy to promote repair of the injured nervous system is the development of efficient non-toxic vectors (see, Blits et al., 2002, p. 593, abstract). Moreover, neuronal cell population targeted by viral vectors is specific. For example, Sinnayah et al., (Hypertension, 2002, p. 604, col. 1, paragraph 1) disclose transduction of neurons and local retrograde transport by feline immunodeficiency virus (FIV) in murine supraoptic nucleus and subfornical organs while adenoviruses (Ad) transduce glial and neuronal populations with distant retroviral transport. Further, short-term expression was observed with Ad, in contrast, minimal decline occurred with FIV transduction. Hence, issues such as efficient-non toxic vectors, safe and efficient gene transfer, targeting of specific cells for treatment of specific type of disease and stability of expression are concerns disclosed in the art at the time of filing of the instant application for an effective method of reducing neuronal cell death in a mammal. Thus prior art teaches the challenges faced in clinical applications of viral

and non-viral gene therapy and the need to use a gene delivery system tailored, as required by the clinical target.

Applicant argues in p. 54 of remarks that 1) the claims do not require prevention of a neurodegenerative disease, and that 2) understanding the mechanism by which any particular neural marker protein reduces neuronal cell death is neither relevant nor required for enablement. Such is not persuasive.

1) Though new amended claims recite the term "reducing" instead of "prevention", any reduction of neuronal cell death intrinsically contributes to prevention of neuronal cell death. 2) Applicant discloses on p.44, paragraph [42], that neuronal cell markers can either be upregulated or downregulated as a result of neuronal cell death. Hence, NM agents can be screened for their ability to decrease or increase cell death. Thus understanding the cellular and molecular mechanisms that govern neuronal survival is critical to enable the design of experiments aimed at non-viral and viral vector-mediated transfer of genes encoding neuronal markers.

Applicant argues on p. 55 " in view of the extensive teaching in the prior art regarding *in vivo* gene transfer in general and the explicit teachings of the specification, the lack of *in vivo* working examples should not be given undue weight". Such is not persuasive.

The examiner has discussed above the unpredictability of the art at the effective filing date of the instant appliciaon (e. g. 2002). As argued in the previous office action, Applicant contemplates in Examples [50] gene expression of genes shown in Table 9, by comparing right to left eye in animals, and in Example [51] gene expression of genes shown in Table 8. However, Applicant disclose no other details in relation to a method of administering a nucleic

acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to reduce neuronal cell death in neurodegenerative diseases.

Thus, the disclosed information from the as-filed application plus the state of the prior art is not deemed sufficient to reasonably convey to one of ordinary skill in the art that the Specification is reasonably enabling for the full breadth of the claim at the time the invention was made, the lack of proper animal models and therapeutic applications in human patients, insufficient guidance and direction in the specification, the inherent unpredictability in the Art, the state of the Art and the nature of the invention, one of ordinary skill in the Art to would be required to perform a large amount of experimentation to make and/or use the invention claimed by the Applicant

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nguyen Dave can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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